CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
CYFLUTHRIN (BAYTHROID)

Chemical Code # 2223, 3956 Tolerance # 50317, 51054

April 19, 1989
Revised 11/06/96,12/05/97, 3/10/00, 6/6/00, 8/28/00, 3/30/04

I. DATA GAP STATUS

Combined, rat:	**No data gap, no adverse effect**
Chronic toxicity, dog:	**No data gap, possible adverse effects**
Oncogenicity, mouse:	**No data gap, no adverse effect**
Reproduction, rat:	**No data gap, possible adverse effect**
Teratology, rat:	**No data gap, possible adverse effect**
Teratology, rabbit:	**No data gap, possible adverse effect**
Gene mutation:	**No data gap, no adverse effect**
Chromosome effects:	**No data gap, no adverse effect**
DNA damage:	**No data gap, no adverse effect**
Neurotoxicity:	**Not required at this time, possible adverse effect indicated**

Toxicology one-liners are attached.
All record numbers for the above study types through 176254 were examined.
**** indicates an acceptable study.**
Bold face indicates a possible adverse effect.
File name: T040330.doc
Revised by T. Moore 3/30/04

FCR 1272 = racemic mixture
FCR 4545 = optically active isomer

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may identify additional effects.

Note: The registered active ingredient is cyfluthrin. Cyfluthrin and beta-Cyfluthrin have different proportions of four diastereomers (I, II, III, IV; see DPR doc. # 50317-149, rec. # 129672, letter dated 4/5/94). Beta-cyfluthrin data have been submitted using cyfluthrin data to fill testing requirements for beta-Cyfluthrin.

COMBINED, RAT

**** 50317-212, 159307; 51054-025, 176254; A Technical Grade Cyfluthrin: "Combined Chronic Toxicity/Oncogenicity Testing Study in Rats," Laboratory Project Study ID 94-272-BK, Report No. 107769; B.S. Wahle and W.R. Christenson; Bayer Corporation, Stilwell, KS; 12/12/97. Groups of Fisher 344 rats were fed dietary mixtures of cyfluthrin (batch no. 4030059/BF9340-71; 93.9 - 95.1% purity) at 0, 50, 225, or 450 ppm for 1 year (25 rats/sex/dose at 0 and 450 ppm, 15 rats/sex/dose at 50 and 225 ppm) or 2 years (55 rats/sex/dose at 0, 50, 225, or 450 ppm (M:2.6, 11.6, 22.8; F: 3.3, 14.4, 28.3 mg/kg/day). Five rats/sex/dose were discarded at the end of week 5. Treatment-related effects were decreased body weight gain at 225 and 450 ppm and increased frequency of alopecia at 450 ppm seen in both sexes and decreased serum triglycerides and cholesterol in males at 450 ppm (NOEL = 50 ppm). There were no treatment-related effects on food consumption/utilization, survival, ophthalmology, hematology, and urinalysis, gross pathology, histopathology, and neoplasia. No adverse effect was indicated. The study was originally unacceptable but was upgraded to acceptable status with submission of an adequate rationale for the doses used (S. Morris 6/11/99; upgraded, Leung 8/23/00).**

50317-011; 002734; "FCR 1272 (Cyfluthrin, the Active Ingredient of Baythroid^{TM}) Chronic Toxicity Study on Rats (2-Year Feeding Experiment)," Report No. 11949; H. Suberg and E. Loeser; Bayer AG, Institute for Toxicology; 7/19/83; cyfluthrin, 50% in Wessalon S pre-mix; 0, 50, 150, or 450 ppm in diets of 65 rats/sex/dose for 2 years; microsomal enzymes measured at 1 week on 5 rats/sex/dose; intermediate necropsy at 1 year on 10 rats/sex/dose; slight decrease in weight gain in both sexes at 150 and 450 ppm; no adverse effect indicated; study unacceptable (no analysis of dose, no rationale for dose, MTD not demonstrated, no individual clinical data); possibly upgradeable; NLH/JG, 7/19/85; one-liner, S. Morris, 11/8/88.

50317-149; 129645: This document contains summaries of studies conducted with cyfluthrin and beta-cyfluthirn. Toxicities of the two compounds were compared to support a rationale for using cyfluthrin data to fill testing requirements for beta-cyfluthrin. A 90-day subchronic study was summarized in which rats were exposed to diets containing beta-cyfluthrin at 0, 30, 125, or 500 ppm (p. 11; Suberg, H., "Subchronic Toxicology Study on Rats" [1986], Mobay Report No. 97492). DPR does not have this study on file. Effects seen in this study were compared to those seen in the chronic cyfluthrin study at DPR doc. # 50317-011; rec. # 002734 (p. 14). A 90-day study inhalation study was summarized (p. 13; Pauluhn, J., "FCR 1272, Study for Subchronic Inhalation Toxicity the Rat for 13 Weeks" [1984], Mobay Report No. 86443). Wistar rats were head-only exposed to cyfluthrin aerosols (63 X 6 hours) at 0.09, 0.71, or 4.52 mg/m^3 (analytical). The reported NOEL was 0.09 mg/m^3 based on clinical signs and reduced weight gain. No worksheets were done (Morris and Gee, 1/30/97).

CHRONIC TOXICITY, DOG

**** 50317-211, 158928; 51054-024, 176253; "Technical Grade Cyfluthrin (FCR 1272): A Chronic Feeding Study in the Beagle Dog," Study Number 94-276-ZR, Report No. 108007; R.D. Jones and T.F. Hastings; Bayer Corporation, Stilwell, Kansas; 1/10/97. Groups of 4 beagle dogs/sex were fed dietary mixtures of cyfluthrin (batch no. 4030059/BF9340-71, 95% purity) at 0, 50, 100, 360, or 640 ppm (reduced to 500 ppm beginning week 8; M: 0, 1.36, 2.43, 10.64 mg/kg/day and 15.47; F: 0, 1.46, 3.61, 10.74 and 17.99 mg/kg/day) for 12 months. Group mean body weights were decreased relative to controls in males at 500 ppm and females at 50, 100, 360, and 500 ppm. Mean ovarian weights were reduced in females at 50, 100, 360, and 500 ppm. A possible adverse effect was indicated by increased incidence of postural reaction deficits and gait abnormalities in both sexes at 360 and 500 ppm groups at 6 and 12 months [NOEL (M/F) = 100 ppm (M: 2.43 mg/kg/day, F: 3.61 mg/kg/day)]. The study was originally unacceptable but subsequently upgraded to acceptable (J Kishiyama and S. Morris, 8/24/99; upgraded, Leung, 8/25/00).**

50317-253, 174035; "Toxicogenetic Study on Idiopathic Epilepsy in a Strain of Beagle Dogs" (R.D. Jones, Study # 96-996-IG, Report # 108012, Bayer Corporation, Stilwell, KS, 2/2/98).

50317-016; 025310; "FCR 1272 Chronic Toxicity to Dogs on Oral Administration," Report no.: 11983; K. Hoffman and B. Schilde, Bayer AG, Toxicology Division, Wuppertal-Elberfeld, F.R.G.; 8/3/83; Mobay No. 86031; cyfluthrin, 51% premix in Wessalon S; Six beagles / sex / group were exposed to 0, 40, 160, or 640 ppm in their diets for 12 months. At 640 ppm, increased incidence of vomiting and pasty to liquid feces were seen in both sexes and the mean final body weight of the males was approximately 90% of controls. Two males in the 640 ppm group exhibited hind limb motor dysfunction characteristic of pyrethroid toxicity. These incidences were transient, occurring only once for each dog following feeding at weeks 36 and 37. No other dose-related abnormalities were observed. The NOEL was 160 ppm based on vomiting, pasty to liquid feces, and motor dysfunction seen at 640 ppm. No adverse effect was indicated. The study is unacceptable because no target organ or clear toxicity were demonstrated in both sexes and individual clinical data were missing. The study is upgradeable with submission of an adequate rationale for the doses used and individual clinical data. Morris, 2/22/89.

> **50317-058; 051445: Addendum to doc. # 50317-016, rec. # 025310. This document contains analysis of test material in feed, individual pathology data, definition of histopathology scoring criteria, survey of therapeutic and prophylactic measures during the study, and individual ophthalmoscopic examinations. Morris, 2/22/89.**

50317-010; 000082; "FCR 1272 Chronic Toxicity on Dogs (Six-month Feeding Experiment)," Report no.: 9991; Hoffmann and Kaliner; 6/81; Mobay No. 69923; cyfluthrin, 47.1% premix in Wessalon; Six beagle dogs/sex/dose were exposed to dietary mixtures of 0, 65, 200, or 600 ppm for 26 weeks. Decreased food consumption and weight gain were seen in both sexes at 200 and 600 ppm. Decreased thymus weights were seen in males at 200 ppm and both sexes at 600 ppm. Increased vomiting and diarrhea were seen in both sexes at 600 ppm. Following feeding, males in the 600 ppm group exhibited transient hind limb motor dysfunction characteristic of pyrethroid toxicity. No other dose-related abnormalities were observed. A possible adverse effect was indicated by the decreased thymus weight at 200 ppm in males. The NOEL for this effect was 65 ppm. The study was unacceptable because analysis of test

article in the dietary mixture and GLP statement were not presented. The study was not upgradeable because the exposure period was only six months. Morris, 4/5/89.

50317-149; 129645: This document contains summaries of studies conducted with cyfluthrin and beta-cyfluthirn. Toxicities of the two compounds were compared to support a rationale for using cyfluthrin data to fill testing requirements for beta-cyfluthrin. The report summarized a 90-day feeding study in dogs (p. 12, Von Keutz, E., "Study of Subchronic Oral Toxicity to Dogs" [1987], Mobay Report No. 98577). Beagle dogs were feed diets containing beta-cyfluthrin at 0, 10, 60, or 360 ppm. This study is not on file with DPR. No worksheet was done (S. Morris and J. Gee, 2/3/97).

Statement: The thymus effects seen in the six-month dog study were not clearly toxicologically significant. No histopathological abnormalities of the thymus were seen in the one-year study. For these reasons no adverse effect was indicated by the thymus effects (Morris, 4/5/89).

ONCOGENICITY, MOUSE

**** 50317-218;162442; "Technical Grade Cyfluthrin: An Oncogenicity Testing Study in the Mouse," Study ID 95-271-DR, Report No.108041; B.S. Wahle and W.R. Christenson; Bayer Corporation, Stilwell, KS; 5/28/98. Cyfluthrin (batch 4030059/BF9340-71, 94 - 95%) was fed in the diets of 56 CD-1 mice/dose/sex for 18 months at nominal concentrations of 0, 200, 750, 1400 (male), or 1600 (female) ppm. The analytical concentrations were 0, 31.9, 114.8, and 232.7 mg/kg/day for males and 0, 38.4, 140.6, and 309.7 mg/kg/day for females. During the first month, 6 mice/dose/sex were removed from the study. Treatment related effects included decreased body weight gains and absolute organ weights in both sexes at 750 ppm, males at 1400 ppm, and females at 1600 ppm; increased incidence of rough coat in males at 1400 ppm and females at 1600 ppm; increased incidences of hunch back, lesion redness, and lesion scabs in females at 1600 ppm; increased incidences of lesions of the ear skin (crusty zones, acanthosis, inflammation, ulcers, debris) in males at 750 and 1400 ppm and females at 1600 ppm; and wet stained ventrus in 1400-ppm males (NOEL = 200 ppm). Treatment-related effects were not seen on survival, hematology, histopathology, or tumor incidence. No adverse effect was indicated. The study was acceptable (S. Morris and J. Gee, 10/6/99).**

50317-012; 002736; "FCR 1272 Chronic Toxicology Study on Mice (Feeding Study over 23 Months at 800 PPM)" Report No. 12035; Suberg and Loeser; Bayer AG, Institute for Toxicology; 8/24/83; Mobay Report No. 86107; cyfluthrin, 50% in Wessalon S pre-mix; 0, 50, 200, or 800 ppm in diets of 50 mice/sex/dose for 23 months; slight decrease in body weight in both sexes, alkaline phosphatase elevated in males; no adverse effect indicated; study unacceptable (no rationale for dose, MTD not demonstrated, no analysis of dose, no individual clinical data, no adrenal or brain weights); NLH/JG, 7/19/85; one-liner Morris, 11/07/88.

REPRODUCTION, RAT

****50317-206 154623; "A Two-Generation Reproduction Study Using Technical Grade Cyfluthrin Administered Via the Diet," Study Number 93-672-UZ, Report 107408; D.A. Eigenberg and L.E. Elcock. Bayer Corporation; 3/8/96. Cyfluthrin (Baythroid technical, Batch No. 2030025, 95%) was fed in the diets of 30 CD Sprague-Dawley rats/sex/group for two generations at 0, 50, 125, or 400 ppm (M:3, 9, 29 mg/kg/day; F[premating/gestation]: 4,**

10, 33 mg/kg/day; F[lactation]: 7, 19, 59 mg/kg/day). F0 adults were exposed for 10 weeks then bred to produce the F1 generation. Selected F1 pups were weaned and placed on treated diet for 10 weeks and then bred to produce the F2 generation. One pup/sex/litter from the first 10 litters/generation was sacrificed on post partum day 4. Non-selected F1 and F2 pups were weaned and sacrificed on post partum day 21. Adult males of both generations were sacrificed after the mating period. Females were sacrificed at weaning/death of their litters, gestation day 24, or day 24 after mating period. All animals except the preweanling pups were exposed continuously from initiation of the study until sacrifice. All adult animals and all pups were necropsied. Tissue samples were collected from all adults and one 4-day-old and one 21-day-old pup/sex/litter from the first 10 litters/generation. There were treatment-related decreases in body weight gain and food consumption in F0 and F1 females at 125 and 400 ppm and increased incidences of splayed hind limbs in lactating F0 and F1 females at 400 ppm. Overall compound ingestion during lactation (7, 19, 59 mg/kg/day) was approximately double that of premating and gestation (4, 10, 33 mg/kg/day) (parental NOEL = 50 ppm). There were no treament-related effects on fertility or fecundity parameters. A possible developmental adverse effect was indicated by treatment-related effects in F1 and F2 pups at 125 and 400 ppm: increased incidences of tremors and decreased male pup body weight gains that persisted in the F1 generation through adulthood (developmental NOEL= 50 ppm). Adequacy of dose was demonstrated by the possible adverse effect. The study was acceptable (J. Kishiyama and S. Morris, 9/8/99).

50317-175; 140849: "Pilot Study to Establish Dose Levels for A Two-Generation Reproduction Study Using Technical Grade Cyfluthrin Administered Via the Diet," Study No. 92-972-SH, Report 107010; D.A. Eigenberg and H.E. Hoss; Bayer Corporation, Stilwell, KS; August 21,1995. This pilot study was submitted to support a rationale for the doses used in a two-generation rat reproduction study (DPR doc. # 50317-206, rec. # 154623). Dietary mixtures of cyfluthrin were fed to groups of 10 CD Sprague-Dawley rats/sex at 0, 50, 150, 400, or 600 ppm (F: premating 4.1,10.5, 27.2, 43.9 mg/kg/day; lactation 7.8, 22.9, 59.6, 95.9 mg/kg/day) for one generation. F0 adults were exposed continuously for 4 weeks and then through a 7-day mating period. F0 males were sacrificed after mating. F0 females were exposed through gestation and lactation until the pups were 21 days old at which time the females and offspring were sacrificed. Treatment-related effects in adult females were: increased incidences of hind leg splaying at 400 and 600 ppm during the second and third weeks of lactation; decreased premating body weight gain at 600 ppm; and decreased gestational body weight gains at 600 ppm and lactational body weight gain at 400 and 600 ppm (parental NOEL = 150 ppm). There was no treatment-related effect on reproductive parameters. A possible adverse effect was indicated by treatment-related tremors and decreased body weight gains in pups at 150, 400, and 600 ppm (developmental NOEL = 50 ppm). Supplemental data (J. Kishiyama and S. Morris, 9/15/99).

50317-006; 002662; "FCR 1272 Multigeneration Study on Rats," Report No. 11870; Loeser and Eiben; Bayer AG Institute of Toxicology, Wuppertal, F.R.G.; 6/8/83; Mobay Report No. 85881; cyfluthrin, stated 50% premix with Wessalon S; Dietary exposures of 0, 50, 150, and 450 ppm were used in a 3 generation reproduction study in which 10 male and 20 female rats were exposed through 2 mating cycles per generation. Each female had an opportunity to mate with 3 males per generation. Pups exposed through lactation period. Pups were culled

to 10 per litter 5 days after birth. The F1a, F2a, and F3a generations were discarded at 4 weeks. F1b and F2b pups were used for subsequent generations. Parental F2bs and 4-week-old F3b pups were necropsied. Histopathology performed on 10 F3b pups per sex. Paternal NOEL = 50 ppm (.20% decrease in weight gain at 150 ppm). Maternal NOEL ≥ 450 ppm. Pup NOEL = 50 ppm (decreased pup viability at 5 days and 4 weeks at 150 and 450 ppm). Possible adverse effects were indicated by pup NOEL ≤ parental NOEL's. Study was unacceptable because insufficient numbers of adults and pups necropsied and examined histopathologically. NLH/JG, 7/16/85; one-liner, Morris, 1/30/89.

50317-010; 000080: This is a partial duplicate of doc. # 50317-006, rec. # 002662. No worksheet was done. Morris, 1/28/89.

50317-058; 051444; "Summary of Diet Analysis Results," Report No. 85881. This is supplemental to DPR doc. # 50317-006, rec. # 002662. No worksheet was done. Morris, 1/28/89.

TERATOLOGY, RAT

**** 50317-202; 149367; "A Developmental Toxicity Study with FCR 4545 Technical in the Wistar Rat," Study Number 95-612-EW, Report Number 107453; A.B. Astroff; Bayer Corporation, Stilwell, KA; 9/4/96. Groups of 30 inseminated female Wistar rats were given cyfluthrin (FCR 4545 Technical, batch 3030125, 97.3%, 1% cremophor vehicle) by oral gavage (10 ml/kg) on gestation days 6 through 15 at nominal doses of 0, 3, 10, or 40 mg/kg/day (analytical dose 0, 2.71, 9.42, or 41.96 mg/kg/day). Dams were sacrificed on gestation day 20, necropsied and ovaries and uteri were examined. Fetuses were sacrificed, examined externally with one half of each litter being examined for skeletal development and the remaining were examined for visceral development. Treatment-related maternal effects were decreased food consumption and body weight gain at 10 and 40 mg/kg/day and hypoactivity, locomotor incoordination, salivation, and death (3/20) at 40 mg/kg/day (maternal NOEL = 3 mg/kg/day). Treatment-related developmental effects were increased preimplantation loss, fetal death, and early resorptions and decreased mean pup weights at 40 mg/kg/day (developmental NOEL = 10 mg/kg/day). There were no treatment-related effects on external, visceral or skeletal malformations or variations. No adverse effect was indicated (developmental NOEL > maternal NOEL). The study was acceptable (S. Morris and J. Gee 10/16/96).**

50317-010; 000079; "FCR 1272 Evaluation for Embryotoxic and Teratogenic Effects on Orally Dosed Rats," Report No. 10562; G. Schluster; Bayer AG Institute of Toxicology, Wuppertal, F.R.G.; 1/20/82; Mobay Report No. 80971; cyfluthrin, batch no. 16001/79, stated 85% purity; Doses of 0, 3, 10, or 30 mg/kg, made up in 5 ml lutrol per kg b.w., were given by oral gavage to 30 inseminated females per dose on gestation days 6 through 15. On gestation day 20, fetuses were harvested by cesarean section and examined for external, visceral, and skeletal abnormalities. High stepping gate was seen in 6 females per group at 10 and 30 mg/kg and ataxia and decreased motility were seen at 30 mg/kg. No dose-related fetal abnormalities were reported. No adverse effects were indicated (maternal NOEL = 3mg/kg; developmental NOEL ≥ 30 mg/kg). MTD for dams was not demonstrated. Study was not acceptable but was upgradeable with submission of individual fetal data, acceptable rationale for doses, and analysis of dosing solutions. NLH/JG, 7/17/85; one-liner, SRM, 1/17/89; revised, J. Gee and S. Morris, 2/2/97).

50317-099; 070057; "FCR 1272, Common Name Cyfluthrin, Study for Embryotoxic Effects on Rats after Inhalation," Report No. 97403; Bayer AG, Toxicology Division, Wuppertal, F.R.G.; 2/1/88; cyfluthrin, 93%; aerosol vehicle of 10 mg/m3 ethanol (vapor) and 10 mg/m3 polyethylene glycol (particles); 30 inseminated female rats / group were nose/head exposed 6 hours / day on gestation days 6 through 15 to aerosol containing analytical concentrations of 0.0, 1.1, 4.7, or 23.7 mg/m3 (trial 1), and 0.0, 0.09, 0.25, 0.59, or 4.16 (30% O_7) mg/m3 (trial 2); 90% of aerosol was $\leq$ 5 um; minor maternal clinical signs and slight weight decrease at 4.16 to 23.7 mg/m3; dose-related, significant decrease in fetal weight at 1.1 to 23.7 mg/m3 and dose-related increase in microphthalmia and anophthalmia at 23.7 mg/m3; possible adverse effect indicated (maternal NOEL $\geq$ 23.7 mg/m3 > developmental NOEL = 0.59 mg/m3 [decreased fetal weight]); study unacceptable (MTD not reached because maternal weight decreased only 7.4% at 23.7 mg/m3 on day 15, no individual fetal data); study upgradeable with submission of adequate rationale for doses and individual fetal data. Parker/Morris, 9/2/88.

50317-017; 025312; "Compilation of the 'Spontaneous Malformations' in the Rat Strain FB 30 (Long Evans) from 1971 - 1980." This document contains historical control data only. No worksheet was done. Morris, 02/24/89.

50317-102; 058999; "Addendum to FCR 1272 Common Name: Cyfluthrin, Study for Embryotoxic Effects on Rats after Inhalation," Report No. 97403-1; Bayer AG, Institute of Toxicology, Wuppertal 1, F.R.G.; 8/16/88: This report contains statements about the mechanism of developmental toxicity seen in the original report. These statements did not alter CDFA's finding of a possible adverse effect (see worksheet). Morris, 04/18/89

50317-102; 059000; "FCR 1272 (Suggested Common Name: Cyfluthrin) Study of the Blood Gases in Rats," Report No. 97408; Bayer AG, Institute of Toxicology, Wuppertal 1, F.R.G.; 8/16/8; Ten male rats / dose were nose- only exposed to cyfluthrin aerosols at 0, 16, 50, or 101 mg/m3 for one, 3-4 hour exposure. No toxicologically relevant changes in the blood gases or acid base status were seen at any dose. Treatment related effects were hypothermia and toxicologically insignificant increases in blood bicarbonate levels at 16, 50 and 101 mg/m3; signs of nose irritation, decreased respiration rates, and decreased arteriovenous shunt at 50 and 101 mg/m3; and decreased arterioalveolar O_7 difference at 101 mg/m3. Data from this report was cited in doc. # 50317-102, rec. # 058999. This report did not alter CDFA's finding of a possible adverse effect (see worksheet). Morris, 04/18/89.

50317-103; 073625; "FCR 1272 (C. N. Cyfluthrin) Study for Correlation of Concentration with Body Temperature (Hypothermia) in the Rat (Exposure 1 X 6 Hours)," Report No. 98563. 10/12/88; Five rats / sex / dose were nose- only exposed to cyfluthrin aerosols at 0, 0.3, 1.0, 3.6, or 25.1 mg/m3 for one, 6-hour exposure and then observed four 14 days. No clinical signs were observed at 0, 0.3, 1.0, or 3.6 mg/m3. At 25.1 g/m3 both sexes showed slight symptoms of reduced motility, piloerection, slowed respiration, and high gaits that cleared by day 1 and an unkempt appearance that cleared by day 2. Significant decreases in rectal temperature were seen in males at 3.6 mg/ml3 and in both sexes at 25.1 mg/ml3 at 5 minutes post exposure with returns to normal values within 2 hours. This report did not alter CDFA's finding of a possible adverse effect. Morris, 04/19/89.

50317-041; 036926; "Embryotoxicity (Including Teratogenicity) Study with FCR 1272 in the Rat," Project No. 019348; Research & Consulting Company AG, Itingen, Switzerland; 12/14/83; Mobay Report No. 86477; cyfluthrin, batch 816 170 019, 93.4% purity; Pregnant female Wistar KFM-Han rats, 21 to 25 per group, were dosed by oral gavage on pregnancy days 6 through 15 with 0, 1, 3, or 10 mg/10 ml 1% cremophor EL/kg. The dams were sacrificed and necropsied on pregnancy day 21. One-third of the fetuses from each litter were stained and examined for visceral abnormalities and 2/3 were cleared, stained, and examined for skeletal defects. No dose-related effects were seen in the dams or fetuses. No adverse effect was indicated. The study was not acceptable because an MTD was not demonstrated for the dams. The study is possibly upgradeable with submission of an adequate rationale for the doses used. Morris, 2/27/89.

> **50317-087; 067805: This is an exact duplicate of doc. # 50317-041, rec. # 036926. No worksheet was done. Morris, 2/28/89.**
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> **50317-141; 123789; "Supplement: Justification for the Dose Selection for the Oral Embryotoxicity Study With FCR 1272 in Rats", Project 019348; B. Holzum; Research and Consulting Company AG, 4452 Itingen, Switzerland; 3/12/93; Miles Report No. 86477-1: This document contains a dose-finding study, a summary of studies on cyfluthrin toxicity and a rationale for the doses used in the study at doc. # 50317-041, rec. # 036926. Evaluation of these data did not result in a change in study status (see DPR Response, 11/05/96). No worksheet was done (S. Morris, 11/05/96).**

**** 50317-154; 132729; "Inhalation Study for Embryotoxic Effects in Rats", Study No.: T3041008; B. Holzum; Bayer AG, Fachbereich Toxicology, Wuppertal, Germany; 10/5/93. Groups of 25 pregnant female Wistar rats (26 for the 2.55 mg/m^3 group) were exposed by nose-only inhalation to cyfluthrin (FCR 1272, batch no 238005176, 96.2% stated purity, air/ethanol/polyethylene glycol vehicle) at 0 (air), (0 vehicle), 0.46, 2.55, 11.9, or 12.8 mg/m^3 for 6 hours/day on gestation days 6 through 15. The oxygen level was adjusted to 39% for the 12.8 mg/m^3 group. The fetuses were delivered by Cesarean section on gestation day 20. Maternal signs of toxicity included: decreased food consumption and body weight gain at 0.46, 2.55, 11.9, and 12.8 mg/m^3; bloody snout, ungroomed fur at 2.55, 11.9, and 12.8 mg/m^3; respiratory disturbances and hypoactivity at 11.9, and 12.8 mg/m3; and high-stepping gait and salivation at 11.9 mg/m^3. Satellite groups of 5 females/treatment showed hypothermia and hypoventilation at 0.46, 2.55, 11.9, and 12.8 mg/m^3 (maternal NOEL < 0.46 mg/m^3). A possible adverse developmental affect was indicated by decreased placental and fetal weights and increased fetal malformations at 2.55, 11.9, and 12.8 mg/m^3 (developmental NOEL = 0.46 mg/m^3). Developmental effects were decreased in the 12.8 mg/m^3 group with supplemental oxygen. The study is acceptable (J. Gee and S. Morris, 11/6/95).**

> **50317-154; 132728; "Explanatory Report on Results and Mechanistic Studies for Embryotoxic Effects in Rats after Inhalation", Report No. 23219; B. Holzum; Bayer AG Fachbereich, Wuppertal-Elberfeld, Germany; 8/12/94: This document contains a summary of the study at DPR doc. # 50317-154, rec. # 132729 and other related studies submitted in support of a mechanism for the possible adverse developmental affect. No worksheet was done (S. Morris, 11/6/95).**
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> **50317-154; 132730; "Determination of the FCR 1272 Concentration in the Plasma of Rats Following Inhalation Exposure", Report No.: 22726; U. Scmidt; Bayer AG Fachbereich, Wuppertal-Elberfeld, Germany; 12/2/93: This document contains data**

submitted in support of a mechanism for the possible adverse developmental affect seen in the study at DPR doc. # 50317-154, rec. # 132729. No worksheet was done (S. Morris, 11/6/95).

50317-154; 132731; "Pilot Study for Acid-Base Status Following Inhalation Exposure to the Rat", Report No.: 21865; J. Pauluhn; Bayer AG Fachbereich, Wuppertal-Elberfeld, Germany; 11/24/92: This document contains data submitted in support of a mechanism for the possible adverse developmental affect seen in the study at DPR doc. # 50317-154, rec. # 132729. No worksheet was done (S. Morris, 11/6/95).

50317-154; 132744; "Study for Acute Oral Toxicity in Rats", Report No.: 19852; W. Bowmann; Bayer AG Fachbereich, Wuppertal-Elberfeld, Germany; 1/11/91: This document contains data submitted in support of a mechanism for the possible adverse developmental affect seen in the study at DPR doc. # 50317-154, rec. # 132729. No worksheet was done (S. Morris, 11/6/95).

TERATOLOGY, RABBIT

50317-010; 002732; "FCR 1272 Study of Embryotoxic and Teratogenic Effects on Rabbits after Oral Administration," Bayer Report No. 11855; Roetz; Bayer AG Institute of Toxicology, Wuppertal, Germany; 06/01/83; Mobay Report No.85879; cyfluthrin, batch No. 816170019, stated purity 95%, dispersed in aqueous 0.5% Cremophor EL emulsion; Doses of 0, 5, 15, or 45 mg/kg were given by oral gavage to 15 inseminated female Himalayan rabbits per dose on gestation days 6 through 18. Sacrifice and Cesarean section occurred on gestation day 29. At 45 mg/kg, 2 females spontaneously aborted and complete resorption of fetuses occurred in 1. No external, visceral, or skeletal malformations were observed in fetuses. No adverse effect was indicated (maternal NOEL = 15 mg/kg [fetal abortion and resorption at 45 mg/kg] < fetal NOEL $\underline{\geq}$ 45 mg/kg). The study was unacceptable but upgradeable with submission of individual fetal data. NLH/JG, 7/17/85; one-liner Morris, 01/11/89.

50317-017; 025311; "Chemical Safety Data / Historical Control Data for Teratogenicity Studies in Rabbits." This document contains historical control data only. No worksheet was done. Morris, 02/24/89.
50317-017; 025313; "Compilation of the 'Spontaneous Malformations' on Himalayan Rabbits from 1971 until 1980." This document contains historical control data only. No worksheet was done. Morris, 02/24/89.

**** 50317-134; 121287; "Embryotoxicity Study (Including Teratogenicity) with FCR 1272 in the Rabbit", RCC Project No. 309914, Miles No. 103980; H. Becker and K. Biedermann, RCC, Research & Consulting Company LTD., Itingen, Switzerland; 12/3/92. Cyfluthrin (FCR 1272, batch # 238005176, 96% purity, corn oil vehicle) was given by oral gavage to groups of 16 mated female Chinchilla rabbits at 0 (corn oil), 20, 60, or 180 mg/kg/day on gestation days 6 through 18. The does were sacrificed on an gestation day 28 and the fetuses removed by Caesarean section. Gross necropsies were performed on the does with particular emphasis on the reproductive organs. All fetuses were examined for gross external and internal abnormalities and cranial ossification. Heads from half the fetuses were removed and examined by serial section. The headless and intact carcasses were cleared and stained for skeletal examination. Decreased food consumption and transient**

body loss were seen in does at 60 and 180 mg/kg/day. Group mean body weights for all treatment groups were always within 95% of controls (maternal NOEL = 20 mg/kg/day, reduced food consumption and transient body weight loss at 60 and 180 mg/kg/day). A possible adverse effect was indicated by increased post-implantation loss at 60 and 180 mg/kg/day (developmental NOEL = 20 mg/kg/day). The study was acceptable (H. Green and S. Morris, 9/1/95).

50317-140; 122790; RCC Project No. 309903, Miles Report No. 103885.
50317-140; 122791; RCC Project No. 316855, Miles Report No. 103996.
These were two dose-range finding studies for the study at DPR doc. # 50317-134, rec. # 121287). In the first study, groups of 5 mated female Chinchilla rabbits were given single daily oral gavages of the test material at 0, 50, 75, or 100 mg/kg/day on gestation days 6 through 18. In the second study, groups of 5 mated female rabbits were given single daily oral gavages of the test material at 0, 150, or 200 mg/kg/day on gestation days 6 through 18. In both studies, the does were sacrificed on gestation day 28 and the fetuses removed by Caesarean section. Gross necropsies were performed on the does with particular emphasis on the reproductive organs. All fetuses were examined for gross external and internal abnormalities and cranial ossification. Food consumption and body weight gain were reduced in does at 150 and 200 mg/kg/day. Group mean body weights for all treatment groups were always within 89% of controls. A possible adverse effect was indicated by increased post-implantation loss at 100, 150 and 200 mg/kg/day. These data were evaluated in the worksheet for DPR doc. # 50317-134, rec. # 121287 (H. Green and S. Morris, 9/1/95)

GENE MUTATION

50317-010; 000089; "Evaluation of FCR 1272 in the Induced Mitotic Crossing Over, Reverse Mutation and Gene Conversion Assay in Saccharomyces Cerevisiae Strain D7," LBI Project No. 20998, Bayer Study No. T 8004536; Litton Bionetics Inc; 9/82; Mobay Report No. 83570; cyfluthrin, batch 816170019 Eg. 3/81, stated 95% purity; Saccharomyces cerevisiae D7 was used to assess cytotoxicity, mitotic non-reciprocal recombination, mitotic reciprocal recombination and reverse mutation. Assays were conducted with and without S9 activation system from aroclor-induced rat livers. Positive controls were ethylmethanesulfonate (1%, no S9) and sterigmatocystin (5 ug/ml, with S9). Cytotoxicity was not seen at 1.22 to 10,000 ug / ml (3.33% DMSO, 2 plates / dose). No dose-related increases were seen in mitotic non-reciprocal recombination, mitotic reciprocal recombination and reverse mutation at 0.000, 0.625, 1.250, 2.500, 5.0, or 10.0 mg/ml (1.67% DMSO, 4 or 5 replicates / dose). No adverse effect was indicated. Study was not acceptable (no repeat trial). Study was upgradeable with submission of repeat trial. NLH/JG, 7/18/85; one-liner Morris, 12/02/88.

50317-010; 002726; "FCR 1272 Microbial Mutagenicity Study," EHR File No. 700; Institute of Environmental Toxicology; 05/17/82; cyfluthrin, stated 95% purity; Reverse mutation rate was measured in Escherichia coli WP2 hcr and Salmonella typhimurium tester strains (TA1535, TA1537, TA1538, TA100, TA98) with and without S9 activation system isolated from Aroclor-induced, male, Sprague-Dawley rat livers. No dose-related increases were seen in revertants at 0.0, 0.010, 0.050, 0.10, 0.50, 1.0, 5.0, 10.0, or 25.0 mg/plate (3.7% DMSO). Appropriate responses were seen with positive controls. No adverse effect was indicated. Study was not acceptable (only 1 trial with 1 replicate / dose / strain). Study was upgradeable with submission of a total of 2 trials with 3 replicates / dose / strain / trial. NLH/JG, 7/18/85; one-liner Morris, 12/12/88.

50317-010; 002731; "FCR 1272 Salmonella/Microsome Test for Detection of Point-Mutagenic Effects," Report No. 9273; Bayer AG Institute of Toxicology, Wuppertal, F.R.G.; 06/27/80; cyfluthrin, batch 16001/79, stated 83.6% purity; DMSO carrier. The histidine-locus, reverse mutation assay was carried out in Salmonella typhimurium tester strains TA 1535, TA 1537, TA 100, and TA 98. The assay was conducted with and without S-9 activation system from Aroclor-induced male rat livers at dose levels of 0, 20, 100, 500, 2500, or 12500; 0, 3000, 6000, or 12000; or 0, 6000, 12000, or 24000 ug per plate. Two plates per group were used. Test material precipitated at 2500 ug per plate. Positive controls were effective. No dose-related increases were seen in revertants. No adverse effect was indicated. Study was not acceptable (only 1 trial at 24000 ug/plate for 3 strains). Study was upgradeable with submission of a total of 2 trials with 3 replicates per dose per strain. NLH/JG, 7/17/85; one-liner Morris, 01/10/89.

50317-010; 002733; "Mutagenicity Evaluation of FCR 1272 in the Reverse Mutation Induction Assay with Saccharomyces Cerevisiae Strains S138 and S211," LBI Project No. 20998, Bayer Study No. T1004269; Litton Bionetics Inc; 5/82; cyfluthrin, batch 816170019 Eg. 3/81, purity not stated; Saccharomyces cerevisiae, strains S138 and S211, were used to assess cytotoxicity and reversion to menthionine prototrophy. Assays were conducted with and without S9 activation system from aroclor-induced rat livers. Positive controls were quinacrine mustard (10 ug/ml, no S9, stain S138), ethylmethanesulfonate (1%, no S9, strain S211) and sterigmatocystin (5 ug/ml, with S9, both strains). Cytotoxicity was not seen at 1.22 to 10,000 ug / ml (3.33% DMSO, 2 plates / dose). No dose-related increases were seen in revertants at 0.000, 0.3125, 0.625, 1.250, 2.500, 5.000, or 10.000 mg/ml (3.33% DMSO, 1 plate / dose / strain). No adverse effect was indicated. Study was not acceptable (only 1 replicate / dose, 1 or 2 trials / strain). Study was upgradeable with submission of a total of 2 trials with 3 replicates / dose / strain. NLH/JG, 7/18/85; one-liner Morris, 12/12/88.

50317-010; 033935; "FCR 1272 Mutagenicity Test on Bacterial System," Report No. 213, EHR File No. 701; Agriculture Chemicals Institute; 01/19/82; gene mutation (842); cyfluthrin, stated 95% purity; Reverse mutation rate was measured in Escherichia coli B/r WP2 $try^{-}hcr^{-}$ and Salmonella typhimurium tester strains (TA1535, TA1537, TA1538, TA100, TA98) with and without S9 activation system isolated from PCB-induced, rat livers. No dose-related increases were seen in revertants at 0.000, 0.005, 0.010, 0.10, 0.50, 1.0, or 5.0 mg / plate. Appropriate responses were seen with positive controls. No adverse effect was indicated. Study was not acceptable (only 2 trials with 1 replicate / dose / strain / trial). Study was upgradeable with submission of a total of 2 trials with 3 replicates / dose / strain / trial. NLH/JG, 7/17/85; one-liner Morris, 12/12/88.

50317-087; 067807; "CHO/HGPRT Mutation Assay in the Presence and Absence of Exogenous Metabolic Activation," Study No.: T4023.332; 9/85; cyfluthrin, 94.7% stated purity; The forward mutation rate of the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus was measured in Chinese hamster ovary (CHO) cells exposed to 0, 3, 5, 7, or 10 ul/ml test material in the presence or absence of S9 metabolic activation system from Aroclor-induced male rat livers. Adequate positive controls were used. No dose-related changes were seen in mutation frequency. No adverse effect was indicated. The study was unacceptable because of lack of independent samples and cytotoxicity was not adequately demonstrated at the highest dose. The study is possibly upgradeable with submission of an adequate rationale for dose levels and submission of data for 2 trials. Morris, 3/3/89.

**** 51054-018; 173735; "C.N. Cyfluthrine K+L (proposed) Mutagenicity Study for the Detection of Induced Forward Mutations in the CHO-HGPRT Assay In Vitro" (Lehn, H., Bayer AG, Fachbereich Toxicology, Friedrich-Ebert-Strabe 217-333, D-5600 Wuppertal 1, FRG, Project ID No. 97481, 6/27/88). Chinese hamster ovary cells (clone CHO-K1-BH_4) were treated for 5 hrs at 37°C with medium containing test article FCR 4545 (Batch No. 16001/85, 99.6%) at concentrations ranging from 0 (DMSO only) to 100 ug/ml, either in the absence or presence of an activating S9 microsomal fraction. After 6 days subculturing to allow for expression of mutations, cells were replated into medium containing 6-thioguanine, to assay for resistant cells that had lost function of their HGPRT gene through mutation. Two replicate cultures were treated with each concentration of test article and assayed independently for mutation induction. The positive controls ethylmethanesulfonate (1200 ug/ml, -S9) and dimethylbenzanthracene (20 ug/ml, +S9) were included. Two experimental trials were performed under S9 activating conditions and two under nonactivating. The test article caused no cytotoxicity, even at saturating concentrations (>40 ug/ml). Neither in the absence or presence of S9 did the test article cause a significant, reproducible, and dose-dependent increase in the spontaneous mutation frequency relative to the vehicle-only control. In contrast, positive controls were functional. No adverse effects indicated. Study acceptable (Vidair 3/30/00).**

**** 51054-021; 173738; "FCR 4545, Salmonella/Microsome Test for Point-Mutagenic Effect" (Herbold, B., Bayer AG, Institute of Toxicology, FRG, Project ID No. 95605, 1/7/86). Test article FCR 4545 (Batch No. 16002/84, 98.5% pure) was added to cultures of S. typhimurium tester strains TA98, TA100, TA1535 and TA1537 at concentrations from 0 (DMSO only) to 12,500 ug/plate, both in the presence and absence of an activating S9 microsomal fraction, and assayed for its ability to revert the histidine-requiring phenotype to histidine prototrophy. Four replicate cultures (plates) were used per condition, and two independent trials were run for each tester strain. Exposure to test article, and simultaneous incubation for formation of revertant colonies, was at 37°C for 48 hrs. Positive controls were included for both activating and nonactivating conditions. The test article caused no bacterial killing. In addition, the test article did not cause a doubling of the background reversion frequency (negative control) at any concentration tested, nor was there any indication of a dose-response for increased reversion frequency. In contrast, positive controls were functional. It was concluded that the test article is not a mutagen in this assay. No adverse effects indicated. Study acceptable (Vidair 3/31/00)**

CHROMOSOME EFFECTS

50317-010; 002729; "FCR 1272 Dominant Lethal Test on Male Mouse to Evaluate FCR 1272 for Mutagenic Potential," Report No. 9678; Bayer AG Institute of Toxicology, Wuppertal, F.R.G.; 01/07/81; chromosome effects (843); cyfluthrin, batch 16001/79, stated 83.6% purity; 0 or 30 mg/kg were given by oral gavage to 50 male rats / dose. Beginning on dosing day, each male rat was serially mated to 12 females for 4 days each. Experiment was repeated with 0, 30, or 60 mg/kg and 3 serial matings. No dose-related dominant lethal effect. No adverse effect was indicated. The study was unacceptable and not upgradeable due to lack of concurrent positive controls. NLH/JG, 7/17/85; one-liner, Morris, 1/6/89.

50317-010; 002730; "FCR 1272 Micronucleus Test on Mouse to Evaluate FCR 1272 for Mutagenic Potential," Report No. 9435; Bayer AG Institute of Toxicology, Wuppertal, F.R.G.; 09/22/80; cyfluthrin, batch 16001/79, stated 83.6% purity; Two oral doses of 0, 7.5, or 15 mg/kg were given 24 hours apart to 5 mice / sex / dose. Six hours after the second dose,

1000 polychromatic erythrocytes / mouse from bone marrow smears were scored for micronuclei. Positive controls were appropriate. No adverse effect was indicated. The study was unacceptable and not upgradeable because the highest dose group showed no toxicity and single sacrifice time. NLH/JG, 7/17/85; one-liner, Morris, 1/6/89.

**** 50317-087; 067806; "Sister Chromatid Exchange Assay in Chinese Hamster Ovary (CHO) Cells," MA Study No.: T4023.334; Microbiological Associates, Inc., Bethesda, MD; 9/30/85; cyfluthrin, 94.7% stated purity (rec. # 067807), batch # 3-03-0143; The SCE assay was carried out in duplicate at 0, 3, 5, 10, and 20 ug/ml without S9 activation system and at 0, 125, 250, 500, and 1000 ug/ml with S9. Without activation, decreased viability was observed at 10 ug/ml and retarded cell cycle at 20 ug/ml. With activation, no cytotoxic effects were observed but the solubility was exceeded at 1000 ug/ml. No dose-related increases in sister chromatid exchanges were seen. No adverse effect was indicated. The study was acceptable. Morris, 3/13/89.**

**** 50317-128; 114692; "In Vitro Cytogenetic Study with Human Lymphocytes for the Detection of Induced Clastogenic Effects", Report No. 98471; B.A. Herbold; Bayer AG, Institute of Toxicology, Germany, 11/11/88. Samples of human lymphocytes from one male and one female were treated with cyfluthrin (FCR 1272, 95.1% stated purity, DMSO vehicle) at 0, 500, 1000, or 5000 ug/ml (trial 1); 0, 500, 1000, or 2000 ug/ml (trial 2); or 0, 1000, 2000, or 4000 ug/ml. Samples co-incubated with S9 metabolic activation (9000 g supernatant from Aroclor 1254 induced male Sprague-Dawley rat, liver homogenates) were exposed for 2.5 hours followed by 19.5 hours of medium alone. Samples not co-incubated with S9 were continuously exposed to the test material for 24 hours. Colcemid was added at a final concentration of 0.4 mg/ml to all samples for the last 3 hours of incubation. Metaphase spread preparations were made from one sample/dose/sex. One hundred metaphases/sample were evaluated for chromosome aberrations. There were no treatment-related increases in chromosome aberrations. Adequacey of dosing was indicated by decreased mitotic index and precipitation of the test material at ≥ 500 mg/ml. The positive controls were adequate. No adverse effect was indicated. The study is acceptable (H. Green and S. Morris, 8/10/95).**

**** 51054-012; 173728; "FCR 4545, In Vitro Cytogenetic Study with Human Lymphocytes for the Detection of Induced Clastogenic Effects" (Herbold, B., Bayer AG, Institute of Toxicology, D-5600 Wuppertal 1, FRG, Project ID No. 98361, 9/6/88). Cultured human lymphocytes from a male and female volunteer, stimulated to proliferate by addition of phytohaemagglutinin for 48 hrs, were treated with test article FCR 4545 (Batch No. 16001/85, 98.8% pure) at 500, 1000 and 5000 ug/ml, in the absence or presence of an S9 microsomal fraction. Exposure to FCR 4545: 24 hrs in the absence of S9 activation and 3 hrs in the presence of S9 activation. After twenty one hrs, cultures were treated with colcemid (0.4 ug/ml) for 3 hrs. Two hundred metaphase cells (100 per sex) were scored per test article concentration, with or without added S9. Positive controls were 0.15 ug/ml of mitomycin C (-S9) and 15 ug/ml of cyclophosphamide (+S). The highest concentration of test article (5000 ug/ml) lowered the mitotic index by 17% (-S9) and 36% (+S9) relative to the negative controls. Neither in the presence or absence of S9 was there a significant effect of test article on the % of metaphase cells with aberrations (either including or excluding gaps), the % of metaphase cells with exchanges, or the % of polyploid cells. In contrast, the mitomycin C positive control was functional for both the chromosome aberration and exchange endpoints, and the cyclophosphamide positive control was functional for the aberration endpoints but not for exchanges. Polyploid cells were not induced by any treatment. No adverse effects indicated. Study acceptable (Vidair 3/23/00).**

**** 51054-022; 173739; "Micronucleus Test on the Mouse to Evaluate Clastogenic Effects" (Herbold, B., Bayer AG, Fachbereich Toxicology, Friedrich-Ebert-Strabe 217-333, D-5600 Wuppertal 1, FRG, Project ID No. 97415, 3/24/88). Five male and five female mice [strain Bor:NMRI (SPF Han)] were administered test article FCR 4545 (Batch No. 16001/85, 99.6% pure) by single-dose oral gavage at 80 mg/kg and incubated for 24, 48 or 72 hrs, at which time the animals were sacrificed and their femoral marrow isolated for preparation of blood smears. Animals administered vehicle-only (0.5% aqueous Cremophor) or the positive control substance cyclophosphamide (20 mg/kg) were also sacrificed at 24 hrs. The test article caused no mortality. Clinical signs noted by 24 hrs were apathy, digging and grooming movements, uncoordinated movement, staggering gait, rolling over, retching movements and salivation. At least 1000 polychromatic erythrocytes (PE) per animal were scored for micronuclei. The numbers of normochromatic erythrocytes (NE) per 1000 PEs were also measured. There was no significant effect of the test article on either the frequency of micronucleated PEs (0.15% for the negative control) or the NE/PE ratio. This was true for all three time points. In contrast, the positive control was functional for the frequency of micronuclei per 1000 PEs. Therefore, the test article was not clastogenic in this assay. No adverse effects indicated. Study acceptable (Vidair 4/6/00).**

DNA DAMAGE

50317-010; 033931; "FCR 1272 Microbial Mutagenicity Study," EHR File No. 700; Institute of Environmental Toxicology, Tokyo; 05/17/82; Mobay Report No. 82343; cyfluthrin, stated 95% purity; The DNA-damaging capability of the test compound was assessed in the "rec-assay" by comparing the effect it had on the growth of a strain of Bacillus subtilis that could repair DNA damage (H17) and a strain that could not (M45). At concentrations of 0, 100, 200, 500, 1000, 2000, 5000, or 10000 ug / disk no effects on the growth of M45 and H17 were observed. The appropriate effects were seen for negative and positive controls. No adverse effect was indicated. The study was unacceptable and not upgradeable (only 1 trial with 1 replicate / dose / strain / trial, no trials conducted in the presence of metabolic activation). NLH/JG, 7/18/85; one-liner Morris, 12/12/88.

50317-010; 002727; "FCR 1272 Mutagenicity Test on Bacterial System," Report No. 213, EHR File No. 701; Agriculture Chemicals Institute; 01/19/82; Mobay Report No. 82344; cyfluthrin, stated 95% purity; The DNA-damaging capability of the test compound was assessed in the "rec-assay" by comparing the effect it had on the growth of a strain of Bacillus subtilis that could repair DNA damage (NIG 17) and a strain that could not (NIG 45). At a concentration of 200 ug/disk no effects on the growth of NIG 45 and NIG 17 were observed. The appropriate effects were seen for the and positive controls. No adverse effect was indicated. The study was unacceptable and not upgradeable (only one dose used, only 1 trial with 1 replicate / dose / strain / trial, no trials conducted in the presence of metabolic activation). NLH/JG, 7/17/85; one-liner Morris, 12/12/88.

50317-010; 002728; "FCR 1272 Cyfluthrin Baythroid - Active Ingredient Pol A_1^-. Test to Evaluate Effects for DNA Damage," Report No. 10450, EHR File No. 784; Bayer AG Institute of Toxicology, Wuppertal, F.R.G.; 9/81; Mobay Report No. 82377; cyfluthrin, batch 816 170 019, Eg. 3/81, stated 95.0% purity; The DNA-damaging capability of the test compound was assessed in the "Pol A_1^- test" by comparing the effect it had on the growth of a strain of Escherichia coli that could repair DNA damage (Pol A+) and a strain that could not (Pol A_1^-). Trials were conducted with and without S9 activation system isolated from

aroclor-induced, male, Sprague-Dawley, rat livers. At concentrations of 0, 62.5, 125, 250, 500, or 1000 ug / plate no effects on the growth of either strain were observed. The appropriate effects were seen for negative and positive controls. No adverse effect was indicated. Study was not acceptable and not upgradeable (only 2 trials with 1 replicate/dose/strain/trial). NLH/JG, 7/17/85; one-liner by Morris, 12/14/88.

**** 50317-087; 067809; "Unscheduled DNA Synthesis in Rat Primary Hepatocytes," MA Study No.: T4023.380; Microbiological Associates, Inc., Bethesda, MD; 12/30/87; Mobay Report No. 90903; cyfluthrin, 94.7% stated purity; Unscheduled DNA synthesis was measured by autoradiographic analysis of the incorporation of 3H-thymidine into the nuclei of primary rat hepatocytes exposed for 18-20 hours to 0, 17, 50, 167, 500, 1667, or 5000 ug/ml. Cytotoxicity was demonstrated at $\geq$ 200 ug/ml. No dose-related increase was seen in radiolabel incorporation into nuclei. Adequate positive controls were done. No adverse effect was indicated. The study was acceptable. Morris, 3/14/89.**

**** 51054-014; 173730; "Mutagenicity Test on FCR 4545 Technical in the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay" (Cifone, M., Hazleton Laboratories America, Kensington, MD, Project ID No. 98585, 9/8/87). Primary cultures of rat hepatocytes were exposed to test article FCR 4545 Technical (Batch No. 16001/85, 99.5% pure) at concentrations ranging from 0 (DMSO) to 1010 ug/ml in the presence of 1 uCi/ml of ^{3}H-thymidine for 18-19 hrs at 37^{o}C. Cells on coverslips were processed for autoradiography and determination of net nuclear grain counts (nuclear grain number minus the average grain number of 3 adjacent nuclear-sized areas of the cytoplasm), while parallel cultures were assayed for cytotoxicity by trypan blue exclusion. 50 cells per coverslip and 3 coverslips per condition were scored for net nuclear grain counts. Two coverslips per condition were scored for cytotoxicity, yielding cell survivals ranging from a low of 50% for the highest dose, up to 96.5% for the lowest dose (relative to solvent-only control). The test article was associated with a few small increases in net nuclear grain counts; however, the largest such increase was only to 1.04 mean net nuclear grains (5.03 ug/ml) compared to 0.57 for the solvent control. In contrast, the positive control (2-acetyl aminofluorene, 0.10 ug/ml) induced a mean net nuclear grain count of 9.76. The mean % of nuclei with >6 net nuclear grains ranged from 0 to 3.3% (at 5.03 ug/ml) for cells exposed to test article compared to 1.3% for the negative control and 75.3% for the positive control. Only cells exposed to the positive control had net nuclear grain counts of >20 (7.3%). It was concluded that the test article was negative in this assay for DNA damage and repair. No adverse effects indicated. Study acceptable (Vidair 3/28/00).**

NEUROTOXICITY

50317-010; 000083; "FCR 1272 Study for Nerve Damage Effect on the Rat after 5-Months Oral Application," Report No. 10705; J. Thyssen and O. Vogel; Bayer AG Institute of Toxicology, Wuppertal, F.R.G.; 3/10/82; Mobay Report No. 82352; cyfluthrin, batch no 16001/79, 83.3% stated purity, dose made up in polyethylene glycol 400; Fifteen rats / sex were treated daily for 5 months by oral gavage with sufficient doses to induce acute toxic symptoms. The doses varied daily between 30 and 80 mg/kg with X daily doses of 64.3 mg/kg for males and 67.7 mg/kg for females. Gross necropsies were performed. Histopathology of liver, kidney, adrenals, brain, spinal marrow, and Nervi ischiadici were done on 5 rats / sex. Two to 4 hours after dosing rats showed behavioral/locomotive disturbances and salivation. Males showed decreased weight gain and increased mortality. No treatment-related neuropathology observed. No adverse effect was indicated. This study was not evaluated for

acceptability because it was not a required test type. No worksheet was done (note: rat used instead of hen, no analysis of test material, no forced motor activity tests, no protective agent, non-guideline dosing schedule, no positive control). Morris, 3/21/89.

50317-010; 000086; "FCR 1272 (Cyfluthrin, Baythroid Active Ingredient) Neurotoxicity Study on Chickens after Cutaneous Administration (Cumulation Tests)," Report No. 10768; Bayer AG Institute of Toxicology, Wuppertal, F.R.G.; 3/29/82; cyfluthrin, 91.4 - 95%; groups of 10 hens were treated cutaneously for varying times and observed 42 days post-treatment; 5000 mg for 23 hours/day for 5 days produced dermal irritation, behavior abnormalities to day 10, and single deaths on days 8 and 15; 5000 mg for 6 hours/day for 5 consecutive days/week for 3 weeks produced dermal irritation, behavioral effects that diminished with time, and no deaths; no signs of delayed neurotoxicity; no adverse effect indicated; study not evaluated for acceptability because it is not a required test type at this time (note: no analysis of test material, no positive control, no rationale for exposure protocols, no forced motor activity tests); NLH/JG, 7/19/85; one-liner by Morris, 11/9/88.

50317-010; 000087; "Neurotoxicity of Single Doses of FCR 1272, NAK 1472, or NAK 1654 in Adult Hens", Mobay No. 86011; Mobay Chemical Corporation; 3/9/81; cyfluthrin, batch # 16003/79, lot # 02263, purity not stated, in Carbowax; 10, 17-month-old hens were given single 5000 mg/kg oral doses and observed 56 days; positive controls were single oral doses of 500 mg TOCP/kg given to 10 hens; test group had 1/10 mortalities, slight weight loss with recovery, no signs of delayed neurotoxicity; no adverse effect indicated; study not evaluated for acceptability because it is not a required test type at this time (note: no analysis of test material, no 21-day dose, no forced motor activity tests, no negative controls, no protective agent, 9/10 positive controls died, no individual data); NLH/JG, 7/18/85; one-liner by Morris, 11/10/88.

50317-010; 033934; "Neurotoxicity of Repeated Doses of FCR 1272 in Adult Hens", Mobay No. 86011; Mobay Chemical Corporation; 3/9/81; cyfluthrin, batch # 16005/80, 89.3%, in Carbowax; 10, 17-month-old hens were given two 5000 mg/kg doses seven days apart and observed 49 days; positive controls were single doses of 500 mg TOCP/kg given to 5 hens; 2/20 mortalities, no signs of delayed neurotoxicity; no adverse effect indicated; study not evaluated for acceptability because it is not a required test type at this time (note: no analysis of test material, no 21-day dose, no forced motor activity tests, no protective agent, 5/5 positive controls died, only 4 negative controls, no individual data, route of exposure not stated); NLH/JG, 7/18/85; one-liner by Morris, 11/10/88.

50317-010; 000088; "FCR 1272 Neurotoxicity Studies on Hens: Single Oral Application," Report No. 9753; Bayer AG Institute of Toxicology, Wuppertal, F.R.G.; 1/27/81; cyfluthrin, batch 16001/79, lot # 2151, 85.3%, 20 - 25% emulsion in polyethylene glycol; 10 to 25, 15-to-20-month-old hens were given single oral doses of 1000, 2500, or 5000 mg/kg and observed for 19 to 42 days; mortalities were 6/10 at 2500 mg/kg and 10/25 at 5000 mg/kg; dose-dependent behavioral changes were seen up to day 6 at 2500 and 5000 mg/kg; histopathological changes seen in nervous tissue of mortalities; no adverse effect indicated; study not evaluated for acceptability because it is not a required test type at this time (note: no analysis of test material, no 21-day dose, no forced motor activity tests, no protective agent, no positive controls, no negative controls, no individual data, histopathology data on only 2 hens); NLH/JG, 7/18/85; one-liner by Morris, 11/14/88.

50317-010; 033932; "FCR 1272 Neurotoxicity Studies on Hens: Two Oral Applications at 3-Week Interval," Report No. 9753; Bayer AG Institute of Toxicology, Wuppertal, F.R.G.; 1/27/81; cyfluthrin, batch 16003/79, lot # 2263, 84.8%, 20 - 25% emulsion in polyethylene glycol; 30, 15-to-20-month-old hens were given oral doses on days 0 and 21 of 5000 mg/kg and observed until days 42 to 63; positive control consisted of triorthocresylphosphate given orally at 375 mg/kg to 5 hens; behavioral changes were seen up to 3 days after dose 1; 4 hens died and behavioral changes were seen up to 2 days after dose 2; onsets of uncoordinated leg movements and paralysis of legs were seen in 4 hens between days 13 and 20 after dose 2; fiber degeneration of Nervi ischiadici was seen in 10/12 hens; possible adverse effect indicated by signs of delayed neurotoxicity; study not evaluated for acceptability because it is not a required test type at this time (note: no analysis of test material, only 1 dose level, no forced motor activity tests, no protective agent, no negative controls, histopathology done on only 12/30 hens, no individual data); NLH/JG, 7/18/85; one-liner by Morris, 11/30/88.

50317-010; 033933; "FCR 1272 Neurotoxicity Studies on Hens: Five Oral Applications within One Week," Report No. 9753; Bayer AG Institute of Toxicology, Wuppertal, F.R.G.; 1/27/81; cyfluthrin, batch 16003/80, lot # 2241, 94.3%, 20 - 25% emulsion in polyethylene glycol; 10, 15-to-20-month-old hens were given oral doses on 5 consecutive days of 5000 mg/kg and observed for up to 42 days; 5/10 hens died; behavioral changes were seen in 9/10 up to 8 day after initiation of dose; onsets of cramped gaits were seen in 3/6 hens between days 25 and 28; hens were emaciated and had mottled kidneys and brittle livers at necropsy; fiber degeneration of Nervi ischiadici was seen in 6/6 hens; possible adverse effect indicated by signs of delayed neurotoxicity; study not evaluated for acceptability because it is not a required test type at this time (note: no analysis of test material, only 1 dose level, no forced motor activity tests, no protective agent, non-guideline dosing schedule, no positive control, no negative controls, histopathology done on only 6/10 hens, no individual data); NLH/JG, 7/18/85; one-liner by Morris, 11/30/88.

> **50317-044; 040834; "FCR 1272 Neurotoxicity Studies on Hens," Report No. 9753; Bayer AG Institute of Toxicology, Wuppertal-Elberfeld, F.R.G.; 1/27/81. This document contains exact duplicates of CDFA doc. # 50317-010, rec. #'s 033932 and 033933. No worksheet was done. Morris, 3/21/89.**
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> **50317-058; 051446; "Commentary on Report No. 9753 of 27.1.1981"; Bayer AG, Leverkusen, F.R.G; 04/09/85. This document contains statements about findings of neurotoxicity in CDFA doc. # 50317-010, rec. # 033933. Patterson, 12/16/87.**
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> **50317-087; 067813; "Commentary on Report No. 9753 of 27.1.1981"; Bayer AG, Leverkusen, F.R.G; 04/09/85. This document contains an exact duplicate of CDFA doc. # 50317-058, rec. # 051446. No worksheet was done. Morris, 1/31/89.**

50317-030; 025314; "FCR 1272 Special Toxicological Study (Morphological Effects on the Nervous System of Rats)," St. Marianna Medical College; 6/30/83; Mobay No. 86427; cyfluthrin, 95% stated purity, dose made up to 1.6% in polyethylene glycol 400; Fifty male Sprague-Dawley rats were dosed by oral gavage with 40 or 80 mg/kg/day for 14 days (X dose = 60 mg/kg/day). Twenty-five control rats were dosed at 0 mg/kg/day for 14 days. Ten treated and 5 control rats were sacrificed 1, 5, 30, 60, and 90 days after the final dose. Light and electron microscopic examinations were done on selected nervous and skeletal-muscular tissue. All treated animals showed behavioral/locomotive disturbances and salivation that generally lasted < 1 day after dosing. All animals had decreased weight gain during

treatment period. A possible adverse effect was indicated by axonal degeneration of sciatic and femoral nerves seen up to 60 days. This study was not evaluated for acceptability because it was not a required test type. No worksheet was done (note: rat used instead of hen, no analysis of test material, no forced motor activity tests, no protective agent, non-guideline dosing schedule, no positive control). Morris, 2/23/89.

50317-048; 042051; "FCR 1272 Special Toxicological Study (Morphological Effects on the Nervous System of Rats)," St. Marianna Medical College; 6/30/83. This document contains a revised version of CDFA doc. # 50317-030, rec. # 025314. No worksheet was done. Morris, 1/31/89.

50317-087; 067810; "FCR 1272 Special Toxicological Study (Morphological Effects on the Nervous System of Rats)," St. Marianna Medical College; 6/30/83. This document contains an exact duplicate of CDFA doc. # 50317-048, rec. # 042051. No worksheet was done. Morris, 1/31/89.

50317-030; 025315; "FCR 1272 Study for Neurotoxic Effect on Rats after Subacute Oral Administration," Report No. 12338; Bayer AG Institute of Toxicology, Wuppertal-Elberfeld, F.R.G.; 12/27/83; Mobay No. 86305; cyfluthrin, batch 816270030, stated purity 96.5%, dose made up in polyethylene glycol 400; Five rats / sex were dosed by oral gavage with 0, 50 (males only), or 60 mg/kg for 14 days followed by gross pathology and histopathology on selected nervous tissue. From treatment day 2, all animals treated at 50 and 60 mg/kg showed behavioral/locomotive disturbances and salivation. All males treated at 50 and 60 mg/kg showed decreased weight gain. Four males at 60 mg/kg died on days 5-8 and had brain hemorrhages. No treatment-related neuropathology observed. No adverse effect was indicated. This study was not evaluated for acceptability because it was not a required test type. No worksheet was done (note: rat used instead of hen, no analysis of test material, only 2 dose levels, no forced motor activity tests, no protective agent, non-guideline dosing schedule, no positive control, no negative controls). Morris, 3/21/89.

50317-048; 042050; "FCR 1272 Study for Neurotoxic Effect on Rats after Subacute Oral Administration," Report No. 12338; Bayer AG Institute of Toxicology, Wuppertal-Elberfeld, F.R.G.; 10/08/85. This document was an addendum to CDFA doc. # 50317-030, doc. # 025315. No worksheet was done. Morris, 1/31/89.

50317-087; 067814; "FCR 1272 Study for Neurotoxic Effect on Rats after Subacute Oral Administration," Report No. 12338; Bayer AG Institute of Toxicology, Wuppertal-Elberfeld, F.R.G.; 12/27/83. This document contains an exact duplicate of CDFA doc. # 50317-030, rec. # 025315. No worksheet was done. Morris, 1/31/89

50317-044; 040837; "Comments on the Effect of Cyfluthrin on Nerve Tissue with Special Reference to the Health Hazard for User and Consumer;" Bayer AG Institute of Toxicology, Wuppertal-Elberfeld, F.R.G.; 2/22/83: This document contains only comments about various studies on the neurotoxicity of cyfluthrin and no data. No worksheet was done. Morris, 3/22/89.

50317-087; 067811; "Comments on the Effect of Cyfluthrin on Nerve Tissue with Special Reference to the Health Hazard for User and Consumer;" Bayer AG Institute of Toxicology, Wuppertal-Elberfeld, F.R.G.; 2/22/83. This document contains an

exact duplicate of CDFA doc. # 50317-044, rec. # 040837. No worksheet was done. Morris, 1/31/89.

50317-044; 040838; "Study of FCR 1272 on Neuromuscular Dysfunction in the Tilting Plane Test on Rats;" Toxicological Institute of Regensburg, F.R.G.; 5/4/84; cyfluthrin, batch # 070682, purity not stated, dose made up in 2% Cremophor EL; Ten male, Bor:WISW rats / treatment group were dosed by single oral gavage to 0.0, 0.01, 0.03, 0.1, 0.3, or 1.0 mg/kg. At 0.5, 2.0, 5.0, and 7.0 hours after dosing, the neuromuscular functioning of each rat was evaluated using the tilting plane method. Dose dependent decrease in rat coefficient of friction with maximum seen at 5 hours. NOEL = 0.03 mg/kg. No adverse effect was indicated. This study was not evaluated for acceptability because it was not a required test type. No worksheet was done (note: rat used instead of hen, no analysis of test material, no forced motor activity tests, no protective agent, non-guideline dosing schedule, no organophosphate positive control). Morris, 3/24/89.

50317-087; 067815; "Study of FCR 1272 on Neuromuscular Dysfunction in the Tilting Plane Test on Rats;" Toxicological Institute of Regensburg, F.R.G.; 5/4/84. This document contains an exact duplicate of CDFA doc. # 50317-044, rec. # 040838. No worksheet was done. Morris, 1/31/89.

50317-044; 040852; "FCR 1272 Study for Effect on the Neurotoxic Target Enzyme (NTE) with the Chicken (Gallus domesticus)"; W. Flucke and A. Eben; Bayer AG Institute of Toxicology, Wuppertal-Elberfeld, F.R.G.; 9/16/85; Mobay Report No. 90495; cyfluthrin, 92.9% stated purity, dose made up in polyethylene glycol 400; Fifteen hens were dosed by oral gavage with 5000 mg/kg/day. Three hens were sacrificed / day 24 hours after last dose and neurotoxic target enzyme (NTE) activity was measured in brain, spinal cord and Nervi ischiadici. All treated hens died within 3 days. No changes in NTE were seen. No adverse effect was indicated. This study was not evaluated for acceptability because it was not a required test type. No worksheet was done (note: no analysis of test material, only 1 dose level, no forced motor activity tests, no protective agent, non-guideline dosing schedule, 100% mortality). Morris, 3/23/89.

50317-087; 067812; "FCR 1272 Study for Effect on the Neurotoxic Target Enzyme (NTE) with the Chicken (Gallus domesticus);" Bayer AG Institute of Toxicology, Wuppertal-Elberfeld, F.R.G.; 9/16/85. This document contains an exact duplicate of CDFA doc. # 50317-044, rec. # 040852. No worksheet was done. Morris, 1/31/89.

50317-054; 047994; "Acute Delayed Neurotoxicity Study with FCR 1272 (c.n. Cyfluthrin) in the Hen," RCC Project 053008 and 056586; Research & Consulting Company AG, Itingen, Switzerland; 4/11/86; Mobay No. 93094; cyfluthrin, 93.5% stated purity, batch # Pt. 233 590 478, dose made up in polyethylene glycol 400; Twelve hens were dosed with 4300 mg/kg and sacrificed 21 days later (exp. 1). Sixteen hens were dosed on days 0 and 21 with 4300 mg/kg and sacrificed on day 56 (exp. 2). Ten hens dosed on days 0, 1, 2, 3, and 4 with 1500 mg/kg and sacrificed on day 56 (exp. 3). Twenty hens were dosed with 4300 mg/kg and 5 hens were sacrificed at 24, 48, and 72 hours and 7 days (exp. 4). Clinical signs, motor activity, and neurohistology were evaluated in experiments 1-3. Neurotoxic esterase (NTE) was measured in experiment 4. Treated hens ate less, lost weight, and showed behavioral abnormalities. These signs cleared with cessation of exposure. No indication of delayed neurotoxicity or decrease in NTE were seen. No adverse effect was indicated. Positive and negative controls

were adequate. This study was not evaluated for acceptability because it was not a required test type. No worksheet was done (note: lack of protective agent). Morris, 3/24/89.

SUPPLEMENTAL INFORMATION

50317-087; 067796; "Toxicity of Pyrethroids in Warmblooded Animals with Special Reference to Cyfluthrin," Proceedings of the International Conference on Environmental Hazards of Agrochemicals in Developing Countries, Vol. I, pp. 223-240, Alexandria, Egypt; 11/83. This study was not evaluated for acceptability because it was a review article on pyrethroid toxicity. No worksheet was done. Morris, 1/31/89.

50317-044; 040849: Duplicate of 50317-087; 067796.

50317-047; 041775; "4-fluoro-3-phenoxybenzaldehyde (FPBA) Salmonella/Microsome Test to Evaluate for Potential Point Mutation," Report No.: 13429. This was a bacterial mutation assay carried out on an intermediate product in cyfluthrin manufacture. No mutation frequencies were detected at concentrations of 0, 20, 100, or 500 ug/plate. No worksheet was done. Morris, 2/28/89.

50317-087; 067808; "4-fluoro-3-phenoxybenzaldehyde (FPBA) Salmonella/Microsome Test to Evaluate for Potential Point Mutation," Report No.: 13429. This document is an exact duplicate of doc. # 50317-047, rec. # 041775. No worksheet was done. Morris, 3/13/89.

50317-149; 129645: This document contains summaries of studies conducted with cyfluthrin and beta-cyfluthirn: acute toxicity, irritation and sensitization, subchronic, chronic and long term, mutagenicity, and neurotoxicity. Toxicities of the two compounds were compared to support a rationale for using cyfluthrin data to fill testing requirements for beta-cyfluthrin. No worksheet was done (S. Morris, 11/20/95).

50317-149; 129672: This document contains the per cent of isomers I, II, III, and IV in cyfluthrin and beta-cyfluthrin. No worksheet was done (S. Morris, 11/20/95).

**** 50317-195; 148355; "21-Day Dermal Toxicity Study with Technical Grade Baythroid in Rats" (D.L. Warren et. al., Bayer Corp., Agricultural Div., Toxicology, Stilwell, KS, Study # 95-122-ES, 6/6/96). Cyfluthrin Technical (Batch # 2030025/BF9140-23, 95.5% purity) administered dermally to 8 rats/sex/dose for 6hrs/day, 17 and 18 applications over 22 and 23 days for males and females, respectively. 6 dose groups included 0, 0 (2-wk recovery), 100, 340, 1000, and 1000 (2-wk recovery) mg/kg/day. No mortalities were reported. Scabbing were observed at the skin sites from males and females at 1000 mg/kg and females at 340 mg/kg. Crusty zones at the treated skin sites were observed in mid and high dose females as well as high dose males. Possible adverse effects: Abnormal histopathological changes in the skin consisting of moderate to severe ulceration with bordering epidermis thickened by acanthosis and hyperkeratosis were evident in treated skin of 3 males and 7 females in the 1000 mg/kg/day dose group and 1 male and 1 female in the 340 mg/kg/day dose group. After the recovery period, ulceration, hyperkeratosis, acanthosis, inflammation and dermal fibrosis were noted in 1 male and 2 females in the 1000 mg/kg/day dose group. Dermal**

fibrosis was more evident and ulceration less evident at this time period, indicating some progress towards lesion repair. NOAEL (M/F) = NOEL (M/F) = 100 mg/kg/day (based on dermal ulcerations). acceptable. (Leung, 7/30/96).

50317-210; 156562; "Motor Activity Measurements in Male and Female Mice Postnatally Exposed to FCR 1272 (Cyfluthrin) by Inhalation;" (F.W. Jekat, et.al., Bayer AG, Department of Toxicology, D-42096 Wuppertal, Germany; Report No. 107780; 7/23/97); Five dams/group with 4 male and 4 female pups each were exposed to FCR 1272 technical (purity: 96.8%) at concentrations of 0 (vehicle control), 6.0, 15.0, or 58.4 mg/m^3 for 6.3 hours/day for 7 days. The mean MMAD (GSD) were 1.8 (1.8), 1.7 (1.8), 1.7 (1.8), and 1.6 (1.8) μm, respectively. Fourteen weeks later, the pups (now 4-month old adults) were evaluated for treatment-related clinical effects. All of the pups in the 58.4 mg/m^3 group died after the first exposure. At the time of the exposure, no clinical signs were noted in the 6 mg/m^3 group. In the 15 mg/m^3 group, the pups demonstrated decreased motility, poor general condition, tonic seizures, and temporary scratching due possibly to sensory irritation. In the evaluation of spontaneous motor activity 14 weeks later, horizontal activity ($p<0.05$), total distance ($p<0.05$), vertical activity ($p<0.05$), and movement time ($p<0.05$) were increased for the females in the 15 mg/m^3 group. No treatment-related effect was noted upon quinuclidinyl [phenyl-4^{3}H] benzilate (QNB) binding to the muscarinic acetylcholine receptor nor the density of receptor sites. Adverse effect: increased spontaneous activity. NOEL: (M/F) 6 mg/m^3 (based upon the incidence of clinical signs in both sexes at 15 mg/m^3); NOAEL: (M) 15 mg/m^3 (based upon mortality in the 58.4 mg/m^3 group), (F) 6 mg/m^3 (based upon increased spontaneous motor activity levels in the 15 mg/m^3 group). Study supplemental. (Moore, 9/26/97)

50317-009; 002707; "FCR 1272 Short-term Toxicity Tests on Mice (4-Week Feeding and 4-Week Recovery Tests)" (Watanabe, M. et al., Nihon Tokushu Noyaku Seizo K.K., Agricultural Chemicals Institute, Toxicology Laboratory, Report No. 82213, 4/14/82). Technical Cyfluthrin (FCR 1272) (no lot number and purity information provided) was admixed to the feed at dose levels of 0, 300, 1000, or 3000 ppm (0, 43.13, 136.34, and 406.89 mg/kg/day, respectively for males, and 0, 50.36, 164.51, and 432.82 mg/kg/day, respectively for females) and fed to 18 mice per sex per dose level for 4 weeks at which time 12 animals per sex per dose were sacrificed while the remaining 6 animals per sex per dose were observed for an additional 4 weeks. One female at 3000 ppm died during treatment. Ataxia (in males for a short period of time during the treatment period and in females for almost the entire treatment period) and salivation were observed; recovery group animals exhibited no clinical signs during the recovery period. A treatment-related decrease in mean body weight was observed in animals of both sexes sacrificed at 4 weeks and in recovery group males (the first 2 weeks) at 3000 ppm. Treatment-related increases in mean alkaline phosphatase and blood urea nitrogen were observed in male animals sacrificed after treatment at 3000 ppm, with the latter persisting in recovery group animals. Treatment-related increases in mean relative submaxillary gland and kidney weights in both sexes at 3000 ppm and in mean relative liver weight in males at 1000 and 3000 ppm in the animals sacrificed at 4 weeks; these effects were not observed in recovery group animals except for the effect on kidneys in males. Microscopic examination revealed cytoplasmic swelling of the glandular epithelium in submaxillary glands in both sexes at 1000 and 3000 ppm and increased chromatin in the nuclei of hepatocytes in males at 1000 and 3000 ppm and in females at 3000 ppm of animals sacrificed after 4 weeks; none of these effects were observed in recovery group animals. Possible adverse effect indicated: ataxia at the high dose group. NOEL (M)= 43.13 mg/kg/day (300 ppm) and (F)=50.36 mg/kg/day (300 ppm) both based on microscopic

findings. Supplemental study (animals treated for only 4 weeks and no ophthalmological examinations conducted). (Corlett, 12/20/99)

50317-009; 002712; "FCR 1272 Short-term Toxicity Tests on Rats (4-Week Feeding and 4-Week Recovery Tests)" (Watanabe, M. et al., Nihon Tokushu Noyaku Seizo K.K., Agricultural Chemicals Institute, Toxicology Laboratory, Report No. 82212, 3/15/82). Technical Cyfluthrin (FCR 1272) (no lot number and purity information provided) was admixed to the feed at dose levels of 0, 100, 300, or 1000 ppm (0, 8.27, 24.71, and 78.90 mg/kg/day, respectively for males, and 0, 8.44, 25.18, and 77.87 mg/kg/day, respectively for females) and fed to 18 rats per sex per dose level for 4 weeks at which time 12 animals per sex per dose were sacrificed while the remaining 6 animals per sex per dose were observed for an additional 4 weeks. No animals died during the study interval. Straddle gait was observed in both males and females beginning on day 3 of treatment and persisting throughout the 4 week exposure period; recovery group animals exhibited no clinical signs after day 3 of the recovery period. A treatment-related decrease in mean body weight was observed in animals of both sexes sacrificed at 4 weeks and in recovery group males at 1000 ppm. A treatment-related increase in positive urobilinogen and ketone scores was measured during urinalysis at 1000 ppm in animals of both sexes sacrificed after treatment; these effects were not observed in recovery group animals. Treatment-related decreases in mean red blood cell, hemoglobin, and hematocrit levels were observed in both sexes in animals sacrificed after treatment at 1000 ppm; these effects were not observed in recovery group animals. Treatment-related decreases in mean glucose and total protein levels were observed in both sexes in animals sacrificed after treatment at 1000 ppm, persisting to a slight degree in recovery group animals. Treatment-related increases in mean relative submaxillary gland weight in both sexes and in mean relative liver and kidney weights in males at 1000 ppm in the animals sacrificed at 4 weeks; these effects were not observed in recovery group animals. Microscopic examination revealed cytoplasmic swelling of the glandular epithelium in submaxillary glands and a minimal degree of single fiber degeneration of the sciatic nerve in both sexes of animals sacrificed after 4 weeks; none of these effects were observed in recovery group animals. Possible adverse effect indicated: straddle gait and single fiber degeneration of the sciatic nerve. NOEL (M)= 24.71 mg/kg/day (300 ppm) and (F)=25.18 mg/kg/day (300 ppm) both based on clinical signs and microscopic findings. Supplemental study (animals treated for only 4 weeks and no ophthalmological examinations conducted). (Corlett, 12/17/99)

50317-009; 002713; "FCR 1272 Subchronic Toxicity Study on Rats (Three-Month Feeding Experiment)" (Löser, E. and Schilde, B., Bayer AG, Institute of Toxicology, Wuppertal, Germany , Report No. 69544, 6/4/80). 821. Technical Cyfluthrin (FCR 1272) (Batch 16003/79, purity: approximately 84.2%), was admixed to the feed at dose levels of 0 (basal diet only), 30, 100, or 300 ppm (0, 2.24, 7.39, and 22.52 mg/kg/day, respectively, for males and 0, 2.70, 8.83, and 27.97 mg/kg/day, respectively, for females) and fed to 30 Wistar TNO W. 74 rats per sex per dose level for 3 months. No treatment-related mortalities occurred. No treatment-related clinical signs were observed. No treatment-related body weight, hematological, or clinical chemical effects were observed. Microscopic examination revealed no treatment-related effects. No adverse effects. NOEL (M)=22.52 mg/kg/day (300 ppm) and (F)=27.97 mg/kg/day (300 ppm) both based on no effects at HDT. Unacceptable (lack of test diet analysis and justification for dose level selection) and not upgradeable because no ophthalmological examinations were conducted on the test animals. (Corlett, 12/16/99)

50317-009; 002725; "FCR 1272 Subacute Oral Toxicity Study on Rats" (Flucke, W. and Schilde, B., Bayer AG, Institute of Toxicology, Wuppertal, Germany , Report No. 69921, 3/28/80). Technical Cyfluthrin (FCR 1272) (Batch 16001/79, Lo-Nr.: 2151, purity: approximately 85%), dissolved in Lutrol, was administered orally once daily by gavage to 20 SPF-Wistar albino rats per sex per dose at dose levels of 0 (Lutrol), 5, 20, or 80/40 (80 mg/kg during weeks 1 and 3, 40 mg/kg during weeks 2 and 4) for 28 consecutive days. 50% of the animals at each dose level were sacrificed at the end of the treatment period and the remaining 50% were sacrificed at the end of a 6 week post treatment observation period. 6 males and 1 female at 80/40 mg/kg died during the treatment period. No clinical signs were observed in any of the animals in the control, low, and mid-dose groups. Apathy, ruffled coat, dyspnea, salivation, hyperkinesis, ataxia, and athetotic and choreiform movements were observed in both males (beginning on treatment day 3) and females (beginning on treatment days 5-6) at the high dose level with clinical signs severe during weeks 1 and 3 (dose level of 80 mg/kg/day) and minimal during weeks 2 and 4 (dose level of 40 mg/kg/day). After the 28 day exposure period, clinical signs (apathy, ruffled coat) were observed in 80/40 mg/kg/day animals (6 week observation group) up to 7 days following treatment [no individual data]. A treatment-related decrease in mean body weight was observed in males at 80/40 mg/kg/day during treatment with this effect ceasing (in 6 week observation animals) after treatment was terminated. A treatment-related increase in mean alanine aminotransferase levels was observed in both sexes at 80/40 mg/kg/day (animals sacrificed after treatment) but only in males (6 week observation group). Treatment-related increases in mean relative liver (females, animals sacrificed after treatment only) and adrenal (males, animals sacrificed after treatment only and females in both groups) weights were observed at 80/40 mg/kg/day. Microscopic examination revealed no treatment-related abnormalities other than very minimal to minimal diffuse lymphatic hyperplasia in the spleen of 2/5 males at 80/40 mg/kg/day. Possible adverse effect indicated: Ataxia and athetotic and choreiform movements were observed throughout the treatment period at the high dose level. NOEL (M/F)=20 mg/kg/day (based on clinical signs). Supplemental study (animals treated for only 28 days and no ophthalmological examinations conducted). (Corlett, 12/13/99)

RAT METABOLISM

50317-013; 18003; "(Fluorobenzene-UL-^{14}C) FCR 1272: Metabolism Part of the General Metabolism Studies in the Rat"; (W. Ecker; Bayer, Sparte Pflanzenschutz, Anwendungstechnik CE; Study No. 86100; 9/14/83); Four Sprague-Dawley rats/sex/group were dosed with (Fluorobenzene-UL-^{14}C) FCR 1272 (specific activity: 26.9 mCi/mmole, radiochemical purity: 98%; ratio of isomers: 42/58 (cis/trans)) at doses of 0.5 or 10 mg/kg intravenously or orally by gavage. The vehicle used in the study was 5% Cremophor EL in physiological saline. Group A received a single dose of 0.5 mg/kg, intravenously. Group B was dosed orally by gavage with a single dose of 0.5 mg/kg. Group C was dosed orally by gavage with 14 daily doses of 0.5 mg/kg of unlabeled test material, followed by a single dose of 0.5 mg/kg with the radiolabeled test material. Group D was dosed with a single dose of 10 mg/kg of the test material. Urine and feces were collected up to 48 hours post-dose. Between 79.3 and 94.4% of the administered dose was recovered in the urine and feces 48 hours after the dosing. A greater percentage of the radioactivity was recovered in the urine (urine: 57.1 to 70.8% vs. feces: 22.2 to 36.6%). The animals which were dosed iv had between 6 and 8% of the dose still in the body after that time interval. In comparison, those animals which were dosed by gavage had 1.3 to 2.5% of the dose in their bodies. The percentage of radioactivity recovered from either the urine or feces was not particularly affected by the multiple dosing regimen in comparison to the single dose protocol. Administration of the higher dose (Group D) resulted in a slightly greater percentage of

radioactivity being recovered in the feces. Examination of the metabolic profile revealed the predominate moiety to be a conjugated product of FCR 3145 (hydroxylated phenoxy metabolite of 3-phenoxy-4 fluorobenzoic acid) (Metabolite 1). This conjugate represented 35 to 47% of the administered dose and was recovered almost entirely in the urine. A lower percentage of this conjugate was recovered from the urine of Group D (10 mg/kg, single dose) with a corresponding increase in the percentage of the FCR 3191 (3-phenoxy-4-fluorobenzoic acid) being present. Otherwise, none of the parent compound was recovered from the urine and percentages of the other metabolites were quite similar despite the different dosing regimens. Analysis of the fecal samples revealed a greater percentage of the FCR 1272 (parent compound) being recovered in Groups C and D (11 to 19% vs. 0.1 to 0.5% for Groups A and B). This lesser percentage of the parent compound was offset by a greater percentage of unidentified moieties (solids and other) recovered in the feces of the first two groups. Overall, the test material was metabolized by hydrolysis of the substituted dimethylcyclopropane carboxylate moiety and formation of the carboxylic acid (3-phenoxy-4-fluorobenzoic acid). This compound was further hydroxylated and conjugated prior to excretion. **Study supplemental** (study protocol did not fulfill all of the guideline requirements) (Moore, 3/10/04)

50317-007; 2678; "[U-^{14}C] Cyfluthrin ([U-^{14}C]FCR 1272 Fluorobenzene label): Biokinetic Part of the General Metabolism Studies in the Rat"; (O. Klein, H. Weber, and D. Suwelack; Bayer Sparte Pharma; Study No. 85834; 6/9/83); Young adult Mura: SPRA rats were dosed with 0.5 or 10 mg/kg of fluorobenzene-UL-^{14}C cyfluthrin (radiochemical purity: 98%, chemical purity: 97.5%, specific activity: 62 uCi/mg, cis/trans ratio: 42/58). The vehicle used in the study was 5% Cremophor EL in physiological saline. In Group A1, four rats/sex were dosed orally with 10 mg/kg of test material and urine, carbon dioxide and fecal samples were collected up to 48 hours post-dose. In Group A2, five bile duct-cannulated male rats were dosed intraduodenally with 0.5 mg/kg of the test material and urine, bile and fecal samples were collected up to 48 hours post-dose. In Group A, five rats/sex were dosed intravenously with 0.5 mg/kg of the test matrial. In Group B, five rats/sex were dosed orally by gavage with 0.5 mg/kg of the test material. In Group C, five animals/sex were dosed daily by gavage for two weeks with 0.5 mg/kg of unlabeled test material, followed by a dose of 0.5 mg/kg of the radiolabeled test material. In Group D, five rats/sex were dosed orally by gavage with 10 mg/kg of the test material. For the latter 4 groups, urine, plasma and feces were collected periodically up to 48 hours post-dose or in the case of Group C, 48 hours after the last dose. Excretion of radiolabel in the expired air was a negligible excretory pathway due to the placement of the radiolabel on the fluorobenzyl ring. Excretion of the radiolabel through the biliary excretory pathway was significant with 33% of the radiolabel recovered in the bile of the males. These data indicate that at least 85 to 90% of the 0.5 mg/kg dose was absorbed. For the males, 65 to 71% of the orally administered dose was recovered in the urine in comparison to 23 to 33% being recovered from the feces up to 48 hours post-dose. The percentage of radioactivity recovered in the feces increased from 23 to 33% when the dosage was increased from 0.5 to 10 mg/kg. For the females, 53 to 66% of the administered dose was recovered in the urine as compared to 30 to 45% being recovered in the feces. The extremes for the range were for the two groups which received a dose of 10 mg/kg. Residual radioactivity in the body at 48 hours post-dose for the animals dosed orally ranged from 0.5 to 1.4% of the administered dose in the males and 1.2 to 2.1% in the females. The primary site of deposition was in the renal fat. For the animals dosed intravenously, the residual radioactivity in the tissues increased to 5.3 and 6.0% of the dose for the males and females, respectively. In the pharmacokinetic analysis, an absorption half-live and 2 elimination half-lives were determined for the plasma with the absorption half-life ranging from 0.40 to 0.68 hours, the 1st excretory half life from 2.4 to 3.2 hours and the 2nd half-life from 8.5 to 12 hours (oral doses, including both the 0.5 and 10 mg/kg dosing regimens and both sexes except for Group C females). The females

receiving repeated doses of 0.5 mg/kg demonstrated only one elimination half-life of 6.2 hours. There was a lag time of 0.19 to 0.22 hours prior to the absorption of the test material into the systemic circulation. The time to maximal concentration ranged from 1.7 to 2.4 hours for the different dosing regimens. **Study supplemental** (study protocol did not fulfill all of the guideline requirements) (Moore, 3/15/04)

50317-009; 2715; "Comparative Study of Rats on Absorption of FCR 1272 after a Single Oral Administration in Polyethylene Glycol 400 or Cremophor EL/water as Formulation Vehicle"; (A. Eben, K.G. Heimann and L. Machener; Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, Federal Republic of Germany; Study No. 82349; 3/10/82); Fourteen male Wistar rats/group were dosed orally by gavage with 10 mg/kg of FCR 1272 Technical (batch no. 816170019; isomer ratio: I 26.6%, II 19.1%, III 33.7%, IV 20.6%), using either lutrol (polyethylene glycol 400) or 0.1% Cremphor EL in distilled water as the vehicle. At 0.5, 1, 2, 4, 6, 16 and 24 hours post-dose, 2 animals/group were euthanized and samples of blood and the stomach contents of each animal were recovered. These samples were analyzed for the presence of each of the 4 isomers of the test material. The respective vehicles affected the absorption of the test material from the stomach. When introduced in an aqueous vehicle, the test material was present in the systemic circulation within 30 minutes of dosing. In contrast, when the test material was administered in a non-aqueous vehicle, its presence in the blood was first identified at 2 hours post-dose. When the stomach contents were analyzed, the reciprocal relationship was noted in which the animals receiving the aqueous vehicle had a lower concentration of the test material. This circumstance persisted through at least the first two hours post-dose. These results indicate that the vehicle is an important factor in determining the toxic potential of the test material. Study supplemental. (Moore, 3/16/04)

50317-013; 18005; "Fluorobenzene-UL-^{14}C Cyfluthrin (FCR 1272): Biokinetic Study on Rats"; (H. Weber and D. Suwelack; Bayer Pharmaceuticals Division, Wuppertal, Federal Republic of Germany; Study No. 85792; 2/18/83); Young adult Mura: SPRA rats were dosed with 0.5 or 10 mg/kg of fluorobenzene-UL-^{14}C cyfluthrin (radiochemical purity: 98%, chemical purity: 97.5%, specific activity: 62 uCi/mg, cis/trans ratio: 42/58). The vehicle used in the study was 5% Cremophor EL in physiological saline. In Group A, 4 male rats were dosed orally by gavage with 10 mg/kg of the test material and serially sacrificed at 4 time points over a 48 hour period for a whole body autoradiography study. In Group B, 4 male rats were likewise dosed with 10 mg/kg of the test material and urine, feces and carbon dioxide were recovered up to 48 hours post-dose. In Group C, 5 male rats/group were dosed with either 0.5 or 10 mg/kg of the test material intravenously or orally. An additional 5 animals/sex received an oral dose of 0.5 mg/kg of the test material. In Group D, 5 bile duct-cannulated males were dosed intraduodenally with 0.5 mg/kg of the test material. In Group E, a total of 40 male rats were dosed with 10 mg/kg of the test material and 5 animals/time point were serially sacrificed at various time points over a 10 day period. Excretion of radiolabel in the expired air was a negligible excretory pathway due to the placement of the radiolabel on the fluorobenzyl ring. Excretion of the radiolabel through the biliary excretory pathway was significant with 35% of the radiolabel recovered in the bile. These data indicate that at least 85 to 90% of the 0.5 mg/kg dose was absorbed. Otherwise, 56 to 70% of the administered dose was recovered in the urine in contrast to 23 to 37% being recovered from the feces up to 48 hours post-dose. Residual radioactivity in the body was reduced to 8.5 and 2.6% of the administered dose at 24 and 48 hours post-dose, respectively. In the tissue distribution study, the radiolabel was recovered predominantly in the plasma, liver and kidneys through 8 hours post-dose. By 24 hours post-dose, the renal fat demonstrated the highest relative concentration of radiolabel which persisted through to end of the 10 day study. In the pharmacokinetic analysis, an

absorption half-live and 2 excretory half-lives were determined for the plasma with the absorption half-life ranging from 0.52 to 0.55 hours, the 1st excretory half life from 1.8 to 3.2 hours and the 2nd half-life from 8.3 to 12 hours (oral doses, including both 0.5 mg/kg and 10 mg/kg dosing regimens and both sexes). There was a lag time of 0.15 to 0.21 hours prior to the absorption of the test material into the systemic circulation. The time to maximal concentration was 1.5 hours for the two dosing concentrations (0.5 and 10 mg/kg). **Study supplemental** (study protocol did not fulfill all of the guideline requirements) (Moore, 3/12/04)

Although the submitted rat metabolism studies do not individually fulfill the metabolism data requirements established under FIFRA 85-1, collectively, the results are sufficient to fulfill this data requirement.